

BMJ Open HALON—hysterectomy by transabdominal laparoscopy or natural orifice transluminal endoscopic surgery: a randomised controlled trial (study protocol)

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ABSTRACT

Introduction: Natural orifice transluminal endoscopic surgery (NOTES) uses natural body orifices to access the cavities of the human body to perform surgery. NOTES limits the magnitude of surgical trauma and has the potential to reduce postoperative pain. This is the first randomised study in women bound to undergo hysterectomy for benign gynaecological disease comparing NOTES with classical laparoscopy.

Methods and analysis: All women aged 18–70 years, regardless of parity, consulting at our practice with an indication for hysterectomy due to benign gynaecological disease will be eligible. After stratification according to uterine size on clinical examination, participants will be randomised to be treated by laparoscopy or by transvaginal NOTES. Participants will be evaluated on day 0, days 1–7 and at 3 and 6 months. The following data will be collected: the proportion of women successfully treated by removing the uterus by the intended approach as randomised; the proportion of women admitted to the inpatient hospital; postoperative pain scores measured twice daily by the women from day 1 to 7; the total amount of analgesics used from day 1 to 7; readmission during the first 6 weeks; presence and intensity of dyspareunia and sexual well-being at baseline, 3 and 6 months (Short Sexual Functioning Scale (SSFS) scale); duration of surgery; postoperative infection or other surgical complications; direct and indirect costs incurred up to 6 weeks following surgery. The primary outcome will be the proportion of women successfully treated by the intended technique; all other outcomes are secondary.

Ethics and dissemination: The study was approved on 1 December 2015 by the Ethics Committee of the Imelda Hospital, Bonheiden, Belgium. The first patient was randomised on 17 December 2015. The last participant randomised should be treated before 30 November 2017. The results will be presented in peer-reviewed journals and at scientific meetings within 4 years after starting recruitment.

Strengths and limitations of this study

- Randomised controlled trial.
- Blinding of personnel, participants and outcome assessors.
- Relevant patient-reported outcomes.
- Single-centre study.
- Limited generalisability.

Trial registration number: NCT02631837; Pre-results.

INTRODUCTION

Background

The evolution from traditional open surgery to laparoscopic surgery has led to a reduction in surgical morbidity and mortality. Minimally invasive surgical techniques have progressed since the introduction of single-incision laparoscopic surgery (SILS) and natural orifice transluminal endoscopic surgery (NOTES), and are often facilitated by robot assistance.

NOTES is a technique using the natural orifices (mouth, vagina, urethra and rectum) as an access route to the peritoneal cavity for endoscopic surgery. It was described for the first time in 2004 in a porcine model by researchers at Johns Hopkins University.¹ The clinical application of NOTES has been reported in general surgical procedures, such as transgastric appendectomy² and cholecystectomy,³ and demonstrated reduced pain, a shorter length of hospital stay and less complications. Improved cosmetic results due to scar-free surgery in combination with

reduced wound (trocar) complications, supports the increasing use of this new surgical technique.

NOTES has gained popularity among general surgeons, urologists and gastroenterologists over the past few years and its feasibility and safety have been reported.⁴ It can be performed via various entry approaches including the stomach, oesophagus, bladder and rectum. The vast majority of NOTES procedures in women have been performed through the vagina as this allows direct access to the peritoneal cavity.⁵ Culdotomy has been used widely for several surgical procedures involving extraction of large specimens: it has been reported as a safe access that is easy to close afterwards.^{6 7} In hybrid NOTES the surgical procedure is performed through a natural body orifice with transabdominal assistance, whereas the term pure NOTES refers to procedures that involve only transluminal access.

Hysterectomy using a transvaginal NOTES (vNOTES) approach was described for the first time in a human patient by Su *et al*⁸ in 2012.

Objectives and hypotheses

We conducted a systematic review (SR) of the literature by searching MEDLINE, EMBASE and the Cochrane Library from inception to 25 August 2015 using 'Natural Orifice Endoscopic Surgery' and 'hysterectomy' as Medical Subject Headings (MeSH) terms or key words. The results of this SR will be published in 2016; we will adhere to the PRISMA-P guidelines⁹ for writing the protocol of this SR. The protocol has been registered in PROSPERO, the international prospective register of SRs, at the Centre for Reviews and Dissemination (CRD), University of York, UK,¹⁰ with the protocol number CRD42016033023. To the best of our knowledge no randomised controlled studies comparing NOTES with the classical laparoscopic approach for hysterectomy have been reported in the literature: this is the main objective of the hysterectomy by transabdominal laparoscopy or NOTES (HALON) study. A randomised controlled trial (RCT) is a study design that has the advantage to control for all possible known and unknown confounding variables due to the random sequence generation as opposed to observational studies where confounding and bias may be more problematic. High-quality RCTs are generally considered as being the gold standard design for the study of the effectiveness of interventions. The rationale and the objectives of this trial are in accordance with the guidelines of the IDEAL collaboration.^{11–13}

The study hypothesis states that hysterectomy by vNOTES may be at least as effective for removing a non-prolapsed uterus without the need for conversion to an alternative technique compared with the classical laparoscopic approach. A conversion means the use of any other technique than the one allocated by random sequence generation. The following example illustrates a conversion: a study entrant may be allocated to the NOTES group but due to technical problems or a

complication the surgeon decides to switch to laparoscopic, abdominal or vaginal hysterectomy in the interest of the patient. vNOTES may offer several advantages compared with laparoscopy: the avoidance of abdominal scars, more women leaving the day care unit on the day of the intervention and less postoperative pain in the first 7 days following surgery.

METHODS

Trial design and study analysis

This single-centre study is a parallel group RCT conducted at the Department of Gynaecology of the Imelda Hospital in Bonheiden, a general hospital in Belgium serving an estimated population of 150 000 people. A cohort of women aged 18–70 years with a non-prolapsed uterus bound to undergo hysterectomy for benign gynaecological disease will be invited to participate in the study, if eligible. Prior to randomisation, all eligible women will be stratified based on the uterine size on clinical examination: category A=uterine size smaller than 10 weeks of pregnancy, category B=uterine size between 10 and 16 weeks of pregnancy, and category C=uterine size larger than 16 weeks of pregnancy. We considered the size of the uterus to be the most important determinant to affect the primary outcome (successful removal of the uterus). The surgery will be performed by one surgeon (JB) who is equally skilled in operating with both techniques: he has introduced and refined the NOTES approach since November 2013. Our group published three small case series on adnexal removal (N=20),¹⁴ salpingectomy (N=5)¹⁵ and hysterectomy (N=10)¹⁶ performed between November 2013 and February 2015. A non-inferiority study design will be used. The protocol adheres to the SPIRIT standards (<http://www.spirit-statement.org/>) as documented by the SPIRIT checklist that was sent to BMJ Open Editorial Office.

Participants

The HALON trial will recruit eligible women aged 18–70 years, regardless of parity, with a non-prolapsed uterus in need of a hysterectomy for benign indication and who provide informed consent prior to surgery. There is no cut-off for the uterine size to exclude women from participating in the HALON study. Concomitant unilateral or bilateral salpingo-oophorectomy when needed is not an exclusion criterion per se: in our observational personal experience, adnexal masses up to 20 cm diameter can be removed without spilling.¹⁴ Women will be excluded from participation if they present any of the following conditions: history of rectal surgery, suspected rectovaginal endometriosis or malignancy, history of pelvic inflammatory disease, active lower genital tract infection, virginity, pregnancy or failure to provide written informed consent.

Intervention, procedures and standard care

Women in both groups will be admitted to the day care unit on the day of hysterectomy. Clindamycin vaginal cream will be administered on admission.

In the operating theatre, the patient will be placed in the lithotomy position in a vacuum mattress. The abdomen, vulva and vagina will be disinfected with an alcoholic Betadine solution and draped. A Foley catheter will be inserted into the bladder. Cefazolin 2 g and metronidazole 1.5 g will be administered intravenously during the procedure in both groups.

Control group: laparoscopic approach

When randomised to the laparoscopic approach a reusable Hohl uterus manipulator will be inserted through the vagina. A small vertical intraumbilical skin incision will be made. A Veress needle will be inserted into the peritoneal cavity; the correct position of the needle tip will be checked with the Semm test. CO₂ will be insufflated until a maximal intraperitoneal pressure of 15 mm Hg. The Veress needle will then be removed and replaced by a 10 mm reusable trocar. An optic fibre will be inserted through the 10 mm trocar and the peritoneal cavity will be inspected. The woman will be placed in the Trendelenburg position. Three reusable 5 mm trocars will be inserted under direct vision in the left and right iliac fossa lateral of the epigastric vessels, and in the suprapubic region. The small intestine will be gently lifted out of the pelvis using atraumatic forceps. The ureter will be identified, but not routinely dissected unless indicated. The mesosalpinx will be coagulated from lateral to medial using a reusable bipolar grasping forceps and cut using cold scissors. The ovaries will be left untouched or removed based on the absence or presence of pathology as counselled to the patient. The round ligament will be coagulated using a bipolar grasper and cut using cold scissors. The parametria will be opened and the bladder will be dissected from the cervix and cranial part of the vagina. The uterine artery will be coagulated using a bipolar grasper and cut using cold scissors. The same procedure will be repeated on the contralateral side. The vagina will be opened over the cup of the Hohl manipulator using a reusable monopolar hook. The cervix will be excised in a circular fashion using the vaginal cup of the retractor as a backstop. The uterus will be extracted through the vagina. Haemostasis will be performed using a bipolar grasper. The vaginal vault will be closed laparoscopically using three figure of eight vicryl-1 sutures. The peritoneal cavity will be rinsed and haemostasis checked. No drains will be left in the peritoneal cavity unless indicated (difficult haemostasis). The 5 mm trocars will be removed under direct vision. The 10 mm trocar will be removed. The fascial layer will not be sutured. The umbilicus and other incisions will be disinfected with iso-Betadine solution. The skin incisions will be closed using a monocryl 3/0 intradermal suture and steristrips. The wound sites will be covered with a standard bandage. A vaginal pack (Betadine gauze 10 cm×5 m) will be placed to be removed 3 hours later together with the Foley catheter.

Intervention group: NOTES

When randomised to the NOTES approach, three non-therapeutic superficial skin incisions will be made on the same location as in the classical laparoscopic approach. The surgeon will assess whether the anterior and posterior colpotomy and the transection of both sacrouterine ligaments are best performed with either laparoscopic instruments (total vaginal NOTES hysterectomy, TVNH), or with classical instruments for vaginal surgery (vaginally assisted NOTES hysterectomy, VANH).

For VANH

A circular incision will be made around the cervix using a cold knife. The Pouch of Douglas will be opened using a cold scissors. The vesicouterine peritoneum will be opened using a cold scissors. Both sacrouterine ligaments will be cut using a cold scissors and tied off using a vicryl-1 suture. A GelPOINT Advanced Access Platform (Applied Medical) will be used as the vNOTES port and inserted into the peritoneal cavity. CO₂ will be insufflated until a maximal intraperitoneal pressure of 15 mm Hg. An optic fibre will be inserted and the peritoneal cavity inspected. The patient will be placed in the Trendelenburg position. The small intestine will be lifted out of the pelvis.

For TVNH

GelPOINT Mini Advanced Access Platform (Applied Medical) will be used as the NOTES port and inserted into the vagina. CO₂ will be insufflated until a maximal pressure of 15 mm Hg. An optic fibre will be introduced into the pneumovagina. A circular incision will be made around the cervix using a monopolar laparoscopic hook. The Pouch of Douglas will be opened using a cold laparoscopic scissors. The vesicouterine peritoneum will be opened using a cold laparoscopic scissors. Both sacrouterine ligaments will be cut using a laparoscopic bipolar grasping forceps. An optic fibre will be inserted and the peritoneal cavity inspected. The patient will be placed in the Trendelenburg position. The small intestine will be lifted out of the pelvis.

The following steps of the procedure are identical for VANH and TVNH:

The ureter will be identified, but not routinely dissected unless indicated. The uterine and ovarian arteries will be coagulated using a bipolar grasper and cut. The mesosalpinx will be coagulated and cut using a bipolar grasping forceps and a scissors. In women requiring adnexectomy, the infundibulopelvic ligament will be coagulated using a bipolar grasping forceps and cut. Haemostasis will be checked and the peritoneal cavity will be rinsed. The NOTES port and the uterus will be removed through the vagina and the pneumoperitoneum will be deflated. The colpotomy will be closed using a running vicryl-1 suture. A vaginal pack (Betadine gauze 10 cm×5 m) will be placed and removed after 3 hours together with the Foley catheter.

Occasionally, the surgical removal of a benign diseased uterus by any of the two techniques may not be completed according to the random sequence generation because of technical limitations or unexpected findings such as extensive adhesions or unexpected malignancy. Successful NOTES or laparoscopic hysterectomy is feasible in the majority of women, but the probability of success is not readily predictable. In cases where the intended procedure has to be abandoned, the appropriate technique (eg, staging laparotomy for ovarian cancer) or a second procedure (eg, laparoscopy or laparotomy after bowel preparation) under general anaesthesia should be scheduled as soon as possible. Women who require an alternative more appropriate intervention or a second procedure are not excluded or withdrawn from the HALON trial. The investigators will sensitively explain to them that follow-up information is still very important, despite the change in treatment, and unless they wish to withdraw completely from the trial, they will be followed up.

It is anticipated that most women presenting with a suspected benign diseased uterus will require no further intervention other than removal of the uterus with or without the adnexa. However, in some circumstances additional medical treatments may be considered necessary by the responsible clinician at the time of surgery or subsequently. This will be recorded. However, if the need for additional surgery *at the time of surgery* is indicated, then such patients will be excluded for recruitment to the HALON trial. All therapeutic interventions in addition to the removal of the uterus with one or both adnexa will be recorded and as the trial is randomised we anticipate that these further interventions will be symmetrically applicable.

The pain management for both groups will be identical using a standardised protocol developed by the anaesthesiologists involved in the clinical trial. The pain protocol and a printed copy of the study protocol of the HALON trial will be available for consultation in the day care unit, the operating theatre and the recovery room. All steps of the intervention will be discussed with the team during the time-out and specific instruction about analgesics according to the protocol, the time to remove the bladder catheter and the vaginal pack will be noted before sign-out by the anaesthesiologist and the surgeon. The care given by the nurses at the day care unit will be extensively described by a dedicated nurse at the day care unit as a guideline for treating participants in a standardised way.

The decision to discharge the study participant from the day care unit or alternatively to admit her to the in-hospital ward will be primarily decided by the patient based on how she feels following surgery. Both the patient and the outcome assessor (JJAB), who will supervise the discharge, will be blinded to the approach used for the hysterectomy. The outcome assessor will overrule the participant's decision only in her health's interest for example, when vital parameters indicate a life-threatening

condition or based on the presence of complications during the surgical intervention as indicated in the patient record. All study participants will receive a standard list including instructions to avoid sexual intercourse and physical exercise/work for a period of 6 weeks after hysterectomy.

All women will be asked to measure postoperative pain using a Visual Analogue Scale (VAS) twice daily from day 1 to day 7 following surgery, regardless of being at home or in hospital. A dedicated nurse of the day care unit will give detailed instructions to all participants on how to measure the VAS scores. One measurement will be done in the morning after bed rest at night (rest) and the other will be done in the evening before going to bed after physical activity (active). All study participants will note in a pain log book the name, dosage and route of administration of any analgesic drug taken from day 1 to 7.

Outcome measure

We searched the COMET¹⁷ database for a core outcome set for surgery (intervention) in gynaecology (health area) in women aged 18–70 years (target population): we did not retrieve a standardised set of outcomes relevant to laparoscopic hysterectomy.¹⁸

Primary outcome measure

The proportion of women successfully treated by removing the uterus by the intended approach without conversion to another approach will be used as a measure of efficacy.

Secondary outcome measures

The secondary outcomes are as follows: (1) the proportion of women admitted to the in-hospital ward for at least one night observation. Women can decide for themselves whether to leave the day care unit or stay overnight based on how they feel after the surgical procedure. The goal is to recover at home with their family for a fixed period of 6 weeks. The aim of this study was not to examine if participants were able to re-engage in their professional activities sooner with NOTES compared with laparoscopy; (2) postoperative pain scores measured using a VAS¹⁹ twice daily from day 1 to 7; (3) the use of analgesics taken during the first week following surgery; (4) postoperative infection defined by lower abdominal pain with fever >38°C and positive clinical signs or laboratory findings detected during the first 6 weeks of surgery; (5) intraoperative or postoperative complications according to the Clavien-Dindo classification²⁰ detected during the first 6 weeks of surgery; (6) readmission during the first 6 weeks of surgery; (7) frequency and intensity of dyspareunia recorded by the participants at baseline, 3 and 6 months by self-reporting using a simple questionnaire and VAS; (8) sexual well-being at baseline, at 3 and 6 months by self-reporting the Short Sexual Functioning Scale (SSFS). The 'SSFS' is a self-developed questionnaire consisting of four items

that address sexual dysfunctions: decreased sexual desire, dry vagina, orgasmic dysfunction and dyspareunia. Each of these items are scored on a four-point scale ranging from 0 (not or doubtfully present) to 3 (extremely present). Reliability analysis of the SSFS revealed an excellent internal consistency (Cronbach's α 0.92) in two prospective controlled studies on sexual functioning after mastectomy compared with breast-conserving therapy for early-stage breast cancer²¹ and after surgical treatment of vulvar malignancy.²² The SSFS has been used as a research tool in several other publications;^{23–25} (9) the duration of surgery measured in minutes from the insertion of the bladder catheter to the end of vaginal/abdominal wound closure and (10) direct and indirect costs for both techniques incurred up to 6 weeks following surgery.

Recruitment

All women aged 18–70 years, regardless of parity, with a non-prolapsed uterus in need of a hysterectomy for benign indications are eligible for inclusion. We will introduce the trial to all eligible women in the outpatient clinic. A comprehensive, evidence-based patient information sheet will be provided at the clinic visit. Participant information sheets and consent form will be provided in Dutch.

Before the procedure, the women will be given a chance to discuss the risks and benefits of NOTES or laparoscopy for removing the uterus, the process of randomisation and the follow-up requirements with the consultant gynaecologist. It will be carefully explained that the final decision about eligibility will be taken during the surgical procedure and is dependent on the findings; therefore consent will be required before the procedure, in every instance.

Over the past 3 years 504 hysterectomies were performed at the department of obstetrics and gynaecology of the participating centre. The mean number of procedures per year is 168 (\pm SD 19). About 40% of the eligible women should be willing to participate in the proposed study to recruit the required amount of participants within 1 year.

Randomisation and blinding

After stratification according to the uterine size on clinical examination, all participants will be randomly assigned to either the intervention (NOTES) or the control group (laparoscopic technique) using a computer-generated randomisation schedule after stratifying for the size of the uterus. The study secretary will generate the allocation sequence and assign the participants to one of both interventions. Sequentially numbered, opaque, sealed envelopes will be used to ensure allocation concealment.

Trial participants, personnel and the outcome assessor will be blinded to group allocation.

The use of the NOTES technique avoids the use of abdominal incisions. Participants randomised to the

intervention group will have three superficial non-therapeutic skin incisions similar to those routinely done with the laparoscopic technique to blind all study participants, personnel and the outcome assessor. Wound dressings of all the study participants will be left untouched until the postoperative visit on day 7. The practice of performing non-therapeutic skin incisions has been reported in some surgical trials to minimise performance and detection bias when measuring subjective outcomes (eg, pain).²⁶ The decision to use non-therapeutic skin incisions is justified by the risk/benefit ratio of the two interventions under comparison.²⁷

To ensure blinding in case of a suspected adverse event, the outcome assessor will notify the surgeon to assess if a surgical intervention is needed. The participant's allocated intervention will be revealed by the study secretary when the last questionnaires at 6 months have been sent to the Trial office.

Data collection and management

All baseline outcomes and other trial data will be collected paper-based by the outcome assessor, who has been trained and certified in Good Clinical Practice (GCP). We will use the following instruments: VAS for measuring postoperative pain and dyspareunia, the SSFS for measuring sexual well-being with an excellent internal consistency (Cronbach's α 0.92) in two prospective studies^{21 22} and the EQ-5D (Euro Qol descriptive system of health-related quality of life states consisting of five dimensions) which is a widely used and validated tool for measuring health-related quality of life.

We will promote participant retention and complete follow-up by scheduling a first visit 1 week after surgery for collecting pain scores and data on the use of analgesics and a second visit after 6 weeks to collect data on postoperative complications. The study secretary will send reminders to study participants if needed to send the questionnaires at 3 and 6 months. We will collect data on the successful removal of the uterus and admission to the in-hospital ward of women who discontinue prematurely after having been randomised. Women who do not adhere to the follow-up schedule will be contacted by the outcome assessor and will be given an appointment for assessment as soon as possible. We will record the reasons for non-adherence and non-retention because this information can influence the handling of missing data and the interpretation of the study results. To reduce loss to follow-up, we shall record patient's social security number, which allows us to track patients changing GP practice. With postal and telephone reminders we anticipate that, the completeness of data should surpass 90% although, as set out below incomplete follow-up is incorporated into the power calculations.

Owing to the time and costs associated with double data entry, we will use single data entry from the patient's electronic file into paper clinical research forms. This ensures a centralised approach to monitoring data quality and compliance. A computer database

will be constructed specifically for the study data and will include range and logic checks to prevent erroneous data entry. Independent checking of data entry of paper questionnaires will be periodically undertaken on small subsamples by the study secretary. The trial statistician will regularly check the balance of allocations by the stratification variables. Source data verification will only be employed if there is reason to believe that data quality has been compromised.

Statistical methods

Sample size calculation

A sample size calculation was performed for the primary outcome: an appropriate level of statistical power was applied to preclude any clinically important inferiority of NOTES compared with laparoscopy. The assumptions for the conversion rates are based on evidence retrieved from a Dutch prospective cohort study in 42 hospitals including 1534 laparoscopic hysterectomies between 2008 and 2010;²⁸ this study reports a 4.6% conversion rate. We assume that NOTES would be the treatment of choice for the majority of women primarily related to the cosmetic results (no abdominal scars) even if 15% less women had successful removal of their uterus with NOTES compared with the laparoscopic approach. We will conclude non-inferiority when 15% lies above the upper limit of the 95% CI calculated for the difference in the proportion of women successfully treated with either of the two techniques. To achieve 80% power to demonstrate non-inferiority under the assumption of similar success rates of 95% in both groups a sample size of 54 participants (27 women per group) will be required. The target sample size was increased to 64 participants (32 women per group) to account for a drop-out rate of 15%.

We aim to report the actual conversion rates at the end of the study. We predefine that the trial validity is not compromised if the conversion rates are below 10% and similar in both comparison groups. The study design (non-inferiority) is based on the assumption that the conversion rates are similar in both comparison groups, which will be cross-checked at the end of the study.

Statistical analyses

A 95% CI of the difference in the proportions of women with a successful removal of the uterus by the intended technique as randomised will be calculated. Non-inferiority will be concluded when 15% lies above the upper limit of this 95% CI. For this primary analysis, adjustments for prognostic factors will not be made in the first instance. Body mass index (BMI) $>35 \text{ kg/m}^2$, age >65 years, uterine weight 200–500 g or uterine weight $>500 \text{ g}$ have been identified as prognostic factors for the risk of conversion based on the findings of the earlier cited Dutch prospective cohort study;²⁸ the risk of conversion was increased at BMI $>35 \text{ kg/m}^2$ (OR 6.53; $p<0.001$), age >65 years (OR 6.97; $p=0.007$), uterine

weight 200–500 g (OR 4.05; $p<0.001$) and uterine weight $>500 \text{ g}$ (OR 30.90; $p<0.001$). The effect of BMI and age will be explored as a secondary analysis. We aimed to include women without genital prolapse in the HALON trial because we do not consider the NOTES technique to be an alternative for vaginal hysterectomy in women with genital prolapse. Nulliparous women with a narrow vagina could certainly represent an impediment when performing the NOTES technique. In practice NOTES can be done using a VANH or a TVNH approach. The VANH approach is used when the vaginal vault can be reached to open the Pouch of Douglas in a comfortable way. In nulliparous women with a narrow vagina we will use another approach: with the TVNH approach the cervix is circumcised using a monopolar hook and the pouch is opened using laparoscopic scissors. The presence or absence of enough prolapse of the vaginal vault could affect the conversion rates. We will explore this effect in a secondary analysis but we will be very cautious in presenting definitive conclusions for this predefined subgroup analysis: given the limited number of included participants, it is likely that differences even when really present, will fail to reach statistical significance.

Multilevel modelling for repeated measurements will be used to compare the mean differences in VAS pain scores between both comparison groups over all time points, thereby maximising the power of the data available. VAS scores will be transformed if required to meet model assumptions.

Analysis will be performed on an ‘intention-to-treat’ basis in the first instance, as recommended in the Consolidated Standards of Reporting Trials (CONSORT) statement.²⁹ A sensitivity analysis will be performed using ‘per protocol’ data to test the robustness of findings. As a conservative measure, estimates of effect sizes between the two arms will be presented as point estimates with two-tailed 95% CIs.

Descriptive statistics will be used to summarise patients’ characteristics and baseline outcome data in the two treatment groups. Baseline characteristics of the women enrolled in the two groups will be compared to ensure that the randomisation has produced comparable groups of participants, and will be covariates in the modelling procedure.

The statistical significance test for the primary analysis will be one-tailed, and $p<0.05$ will be considered as significant. All tests of the secondary analyses will be two-tailed, and $p<0.05$ will be considered as significant. All statistical analyses will be performed by an experienced biostatistician (AL) who is also a co-investigator in the present research.

The interpretation of missing values in the analysis of clinical trials can be fraught with danger. The methods used to allow for missing data make assumptions about the reasons for data not being present, such as in the ‘observed case’ analysis, where the presence or absence of data is viewed as unrelated to outcome, or in the ‘last observation carried forward’ analysis where the

assumption is that the condition does not improve or worsen following withdrawal from follow-up. To minimise possible biases, participants will continue to be followed up even after protocol treatment violation. Missing data items will be imputed from given values if limited to a single-item response. If a form is missing entirely or is greater than one item imputation will not be attempted. Sensitivity analyses will be carried out to determine whether or not the results obtained are robust to the methods used to handle missing data. Questionnaires will only be treated as late if they are returned after the subsequent questionnaire has been sent to the patient. However, if this form is the only form available at the later time point it will be included at the subsequent time.

Monitoring

HALON is a trial of short duration. Therefore, a data monitoring committee is not needed.

All adverse events reported spontaneously by the participant or observed by the investigator or his staff will be recorded. Infection and peroperative or postoperative complications will be assessed as secondary outcomes until 6 weeks after surgery. We will inform the family physician of all participants in order to assess all possible unintended effects of the trial intervention and promote to report all possible adverse events anonymously using the participant's unique study number to an email address (NOTES@imelda.be). We will use descriptive statistics for data analysis although the trial is not adequately powered to detect important differences in rates of uncommon adverse events. Given the limited resources and the single-centre design there will be no auditing of the conduct of the trial. We will review patient enrolment, consent and eligibility on a regular basis to promote data quality and to preserve trial integrity. The distribution of the allocation to the study groups will be blindly checked by the study secretary at 30%, 60% and 90% of the recruitment and discussed with the study statistician and the principal investigators.

RESULTS

Participant flow diagram

We will show the study flow reported according to the CONSORT statement and checklist in the final report of the HALON trial.²⁹

Recruitment time frame

All women with a non-prolapsed uterus, aged 18–70 years, regardless of parity, in need of a hysterectomy for benign indication and meeting the inclusion criteria will be invited to participate in the trial. Only eligible women with written informed consent obtained before randomisation will be included in the trial.

On the basis of the mean number of hysterectomies performed for benign gynaecological disease in women without genital prolapse at the department of

gynaecology annually (N=168) we estimate that 40% of the eligible women should be willing to participate in the recruit sample size needed (N=64) within 1 year. Based on the follow-up (6 months) and the period of analysis/reporting (6 months) the total study period is estimated to be 2 years.

Data collection

The following patient characteristics will be recorded at baseline: age, BMI, volume of the uterus in weeks, concomitant medication, dyspareunia questionnaire, the SSFS and the EQ-5D questionnaire.

On the day of surgical intervention (day 0) the following data will be collected: duration of the intervention, successful removal of the uterus by the technique as randomised without conversion to another technique with or without cleaving the uterus, admission of the participant to the in-hospital ward for at least one night observation based on her own preference, the total amount of analgesics used at the recovery and day care unit and the maximum VAS pain score on the day 0.

On days 1–7 the pain scores will be collected as reported by the study participant twice daily (1 in the morning and 1 in the evening). The total amount of analgesics used during the first postoperative week will be recorded by the participants and collected by the outcome assessor.

On days 7 and 42 pelvic infection defined by lower abdominal pain with fever >38°C and positive clinical signs or laboratory findings, concomitant medication, readmission and postoperative complications according to the Clavien-Dindo classification detected during the first 6 weeks after the intervention will be assessed and recorded by the outcome assessor.

On months 3 and 6 following surgery the dyspareunia questionnaires, the SSFS questionnaires and the EQ-5D questionnaires will be filled out by the study participants and collected (table 1).

DISCUSSION

Strengths and weaknesses

The main strength of the HALON study is its design as a RCT rather than an observational comparative study. A RCT has the advantage to control for all possible known and unknown confounding variables due to the random sequence generation as opposed to observational studies where confounding and bias may be more problematic. High-quality RCTs are generally considered as being the gold standard for studying the effectiveness of an intervention.

Restricting this single-centre RCT to one surgeon's practice may be considered a major limitation. We nevertheless have carefully balanced the pros and cons of this decision. There can be no discussion on the learning curves or differences in surgical skills among the participating surgeons if all study participants are treated by one surgeon equally skilled at performing both

Table 1 Patient's characteristics and data collection

Data collection	Days												3 months	6 months
	BL	0	1	2	3	4	5	6	7	42				
Age	X													
BMI	X													
Uterine volume	X													
Concomitant medication	X	X	X	X	X	X	X	X	X	X				
Dyspareunia: frequency and intensity	X											X		X
SSFS	X											X		X
Health-related quality of life		X										X		X
Duration of surgery	X													
Successful removal	X													
Admission in hospital (for at least 1 night)	X													
Total amount of analgesics used		X	X	X	X	X	X	X	X					
VAS score		X	X	X	X	X	X	X	X					
Readmission within 6 weeks											X			
Pelvic infection										X	X			
Other postoperative complications		X								X	X			
Direct and indirect costs (up to 6 weeks after surgery)											X			

BL, baseline; BMI, body mass index; SSFS, Short Sexual Functioning Scale; VAS, Visual Analogue Scale.

techniques. A multicentre prospective cohort study could add credibility to the generalisability of the findings, but may pose problems with respect to the learning curves and the differences in surgical skills of the surgeons involved. The aim of the present pilot study is to study the efficacy (Can NOTES work under ideal experimental conditions?). The HALON trial does not address the effectiveness of the new intervention (Does NOTES work in a real-life setting when performed by several surgeons?). Multicentre trials on the effectiveness of NOTES should be carried out when there is evidence of efficacy and after proper training of a larger group of dedicated surgeons as suggested by the IDEAL recommendations.

The conditions in this small efficacy study are experimental and in many instances opposed to 'real-life' conditions: all women are treated by one surgeon equally skilled in using both techniques, women are given better care in this study when compared with standard clinical practice, the dosage of anaesthetic drugs is calculated to limit the possible side effects such as nausea and vomiting that may prevent women leaving the hospital the same day, all outcomes measured are very relevant for women in general, women with adverse outcomes (eg, dyspareunia and sexual dysfunction) will be recalled after the end of the study for counselling and therapy, etc. The results of the HALON trial will therefore have a limited generalisability and their interpretation will be carried out cautiously.

By making three 'non-therapeutic incisions' on the abdomen in the NOTES group it could be argued that this intervention may confound the assessment of the pain outcome. We judged it necessary to blind participants, personnel and the outcome assessor by using these 'non-therapeutic incisions' similar to the ones used in the laparoscopic technique. If we would have

stuck to the pure NOTES technique without scars on the abdominal wall, participants in the intervention arm (NOTES) would have known with certainty that they had undergone the 'new promising technique': this could have introduced substantial bias and would have compromised the internal validity of the HALON trial. After carefully balancing the pros and cons, all the investigators agreed to sacrifice a potential benefit of the NOTES technique (less pain and better cosmetic results by not using abdominal incisions) rather than compromising the study validity by introducing information bias. We accept a possible decrease in the magnitude of a potential benefit and we will report this balanced judgement in the final review.

We considered stratifying for other determinants than the uterine size (BMI and parity) but given the scope and the limitations of this small pilot RCT study we decided to stratify only for the uterine size on clinical examination.

Many outcomes of the present study are patient-reported and patient-centred. The secondary outcome 'the proportion of women admitted to the in-hospital ward for at least one night observation' could equally confound the study results if there would be different and substantial proportions of women wishing to stay for reasons not related to the surgery itself (eg, social reasons) across both comparison groups. Women in the HALON trial can decide for themselves to leave the day care unit or stay overnight based on how they feel after the surgical procedure. The goal is to recover at home with their family for a fixed period of 6 weeks. The aim of this study was not to examine if participants were able to re-engage in their professional activities sooner with NOTES compared with laparoscopy. We admit that the reasons to stay overnight are not necessarily medical. In cases where the reasons to stay overnight was not purely

medical and as such reported by the participant, we noted this as an additional remark in the clinical research file. The primary analysis will be made based on the fact of staying overnight or leaving the day care unit without taking into account the nature of the reasons for staying. We assume that by using the random sequence generation women wishing to stay overnight for social reasons should be equally distributed among both comparison groups. This will be cross-checked if all study data are available. We will do sensitivity analyses if differences are found across the comparison groups for the reasons reported by participants for staying overnight to test the robustness of the data.

Implications for clinical practice

We stress that the HALON trial is a pilot study on the efficacy of the NOTES technique. The two techniques under comparison are performed by one single surgeon (JB) who is equally skilled in using both techniques. The surgeon has been using the new approach since November 2013. During this 2-year period the new technique and suitable instruments used were pilot-tested by the usual 'trial and error' method used for centuries in surgical practice¹³ and adapted into its present form. The feasibility and preliminary safety of the new technique was reported in three observational studies performed in our department^{14–16} in accordance with the principles outlined in the three article series on the IDEAL statement.^{11–13} According to the terminology used by the IDEAL collaboration¹³ this study should be classified as an IDEAL stage 2b trial. The full Patient-Intervention-Comparison-Outcome (PICO) research question is as follows: will a surgeon who is equally skilled at performing both techniques, and beyond his learning curve for the new technique (NOTES), succeed in removing a non-prolapsed uterus in women with benign gynaecological disease at least as often with the new pilot-tested vNOTES approach compared with the standard transabdominal laparoscopic approach without having to convert to an alternative approach? The findings of the HALON study have limited generalisability. Adequate training of other surgeons and more research for example, prospective multicentre prospective cohort studies or large electronic registries will be needed to monitor the long-term outcomes (eg, surgical complications). The reader should be aware that a proof of efficacy by a single-centre pilot study is by itself not sufficient to implement the technique into clinical practice.

We do not consider the NOTES approach as being a more suitable alternative for the vaginal hysterectomy in cases of genital prolapse. The aim of the HALON study is to compare NOTES with laparoscopic hysterectomy in women with non-prolapsed uterus for benign gynaecological pathology. Although NOTES could have been compared with classical vaginal hysterectomy and one might be tempted to consider vaginal hysterectomy as a NOTES technique, our goal was to remove uteri that in a setting outside of the trial would have been removed

by a total laparoscopic approach or open abdominal approach, that is, without sufficient prolapse to do a classical vaginal hysterectomy. The NOTES technique moreover uses a device to create and maintain a pneumoperitoneum in contrast to a vaginal hysterectomy. We hypothesise that gynaecologists will feel more familiar with using NOTES for removing a non-prolapsed uterus compared with performing a total laparoscopic approach: NOTES avoids suturing laparoscopically which requires considerable skill. If the uterus is bulky, the NOTES approach will enable the surgeon more direct access to the uterine blood supply as opposed to the laparoscopic approach. Trying to coagulate the uterine vessels in a bulky uterus filling the pelvic cavity can be quite challenging.

Implications for further research

As suggested by the IDEAL collaboration more research (large multicentre trials performed by adequately trained surgeons in centres of clinical excellence and large prospective registries cumulating data on the safety of the new technique over many years) and adequate surgical training will be needed before NOTES can be offered as a standard daily care surgical practice by a majority of gynaecological surgeons for all women bound to undergo hysterectomy for benign gynaecological disease. HALON should therefore be considered as a necessary kick-off in a long and scientifically rigorous evaluation of a complex surgical intervention. A randomised pilot study on the efficacy of NOTES is needed at this moment in its evolution before this technique becomes widely implemented into daily clinical practice without properly evaluating its potential benefits and harms: the latter scenario is not in accordance with GCP and may harm women in the longer term.

ETHICS AND DISSEMINATION

The HALON trial will be conducted in accordance with the ethical principles set out in the latest version of the 'Helsinki Declaration', the 'Guideline for Good Clinical Practice' and the Belgian Law of 7 May 2004 related to experiments on humans.

A detailed patient information document about the study protocol, the aims of the research and the possible adverse events related to the surgical techniques under comparison will be provided to all eligible women wishing to participate in the trial. We will request written informed consent from all participants before randomisation. This will be obtained by the principal investigator (JB) and the coordinating investigator (JJAB) during a study intake. An adapted informed consent form was drafted based on the template proposed by the Federal Agency for Medicines and Health Products (FAMHP) for clinical research in Belgium.³⁰

The protocol of the HALON trial is registered in ClinicalTrials.gov of the US National Institutes of Health as NCT02631837 (see online supplementary appendix 1

—items WHO Trial Registration Data Set). The study protocol and the informed consent documents (see online supplementary appendix 2—model consent form in Dutch) have been approved by the Ethics Committee of the Imelda Hospital Bonheiden (registration number 689), Belgium on 1 December 2015. The written approval with the Belgian unique study identifier B689201526261 was sent to the FAMHP in Brussels. We will communicate important protocol modifications to the Ethics Committee of the Imelda Hospital, the FAMHP, all trial participants and ClinicalTrials.gov.

The HALON trial is non-commercial and investigator driven. The investigators have taken out an insurance policy for medicolegal responsibility related to the conduct of the study from 1 December 2015 to 30 November 2017 in accordance with Article 29 of the Belgian Law of 7 May 2004 related to experiments on humans.

The clinical research forms and all other study-related documents will be stored securely at the study site in locked file cabinets in an area with limited access. All records that contain names or other personal identifiers will be stored separately from study records identified by a code number. Data collection, storage and dissemination will be in accordance with the Belgian Law of 8 December 1992 on the protection of privacy in relation to the processing of personal data and by the Law of 22 August 2002 on patient rights.

All nine trial investigators (all authors of the protocol of the study) will be given access to the complete final data set at the end of the HALON study.

Offering surgical intervention identified as being most effective or most advantageous after the final analysis of the study data to those women allocated to the other comparison arm is by the nature of the surgical intervention impossible. We will provide post-trial care to those women with identified adverse outcomes in the longer term (dyspareunia or sexual dysfunction) as part of good clinical research practice.

The trial results will be disseminated through scientific journal manuscripts and scientific conference presentations. All investigators will contribute to authorship. We will follow the authorship eligibility guidelines of the International Committee of Medical Journal Editors (ICMJE).

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Contributors JB and JJAB conceived the study. PADM and ILR are responsible for the draft of the pain protocol and the anaesthesia for all trial participants. JJAB, JB, PADM and ILR will be responsible for data collection, quality analysis and storage. PE provided expertise for the sexuality research involved in this clinical trial design. SW provided external review as a content expert. CM provided external peer review on the scientific conduct of the study. AL is responsible for the biostatistics involved in the design and conduct of the trial. BWJM provided external peer review as a methodology expert. All the authors contributed to the refinement of the study protocol and approved the final manuscript.

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HALON—hysterectomy by transabdominal laparoscopy or natural orifice transluminal endoscopic surgery: a randomised controlled trial (study protocol)

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